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Maternal serum screening in the West Bank

An audit of Palestinian and non-Palestinian women having Triple tests - ***Mutaz Akkawi, Rula Ghandour, Abdullatif Husseini, Lamia Halasseh, Qasem Abo Remeleh***

Abstract

Objectives The aim of this second phase of study was to detect or confirm any change in the screening results of Triple tests carried out on Palestinian women living in the West Bank during the period 2004-2010 if compared to that done between 2000-2003.

Methods Data on 1354 pregnant Palestinian and non-Palestinian women living in the West Bank (Filipino women) who were offered the Triple test during the period 2004-2010 were analyzed statistically using the Statistical Package for Social Sciences (SPSS) version 17

Results In this study, out of 1354 subjects, 1267 were eligible for the final analysis. The mean expected age at delivery ± SE (standard error) of the Palestinian women was 27.02±0.17 years compared with 25.5 ±0.2 years in the first study. The AFP results of the Palestinian women tested using AFP MoM cutoff of 2.5 showed that 2.7% had high concentrations compared with only 1.3% in the first study. Filipino women showed the same result for AFP. Our study showed that women with high risk of Down's syndrome were 5% compared with 2.8% in the first phase of study.

Conclusion Our study showed that within about six years there is increase in both the percentage of women with high AFP results and with those with high risk of Down's syndrome which becomes similar to that obtained in the international community. This may be due to direct result of the increase in the mean age of women.

Introduction

Antenatal testing describes procedures performed during pregnancy to detect health problems in the growing fetus. These tests can provide a non-invasive screening for Down's syndrome (trisomy 21) and other congenital anomalies such as spina bifida and anencephaly (neural tube defects – NTDs) through the assessment of maternal serum markers and ultrasonography .1, 2

Down's syndrome (trisomy 21) is the most common cause of severe learning disability in children with an incidence of 1 in 800 live births .3 The incidence of Down's syndrome in some Arab countries exceeds 1.7 per 1000 compared to incidences of 1.0-1.4 per 1000 for other Arab populations .4 As a result of this high incidence, screening and diagnostic tests should be offered. In our community the importance of such tests has been recognized and the first local study on this subject was published in 2005. 5

Screening tests for Down's syndrome are either done in the first or second trimester. 3, 6 First trimester test is usually ordered between 11-13 weeks of pregnancy. This test measures the levels of two serum markers, free β-human chorionic gonadotropin (free β-hCG) and Pregnancy Associated Plasma Protein-A (PAPP-A) in addition to a special ultrasound scan that measures the nuchal translucency (NT) thickness, a space at the back of the baby's neck .7 These tests cannot evaluate the fetus's risk of developing NTDs. First trimester screening is not common in the Palestinian community and efforts are exerted to encourage women to do it in the near future. The most common test done by Palestinian pregnant women is the Triple test. 5

The Triple and Quadruple tests are used to screen in the second trimester of pregnancy between 14 weeks and 20 weeks of pregnancy. It is ordered to help evaluate the risk that a fetus has certain abnormalities, including Down's syndrome and NTDs.7, 8 The Triple test measures the levels of three markers in the serum of the pregnant women: Alpha-fetoprotein (α-FP), Human Chorionic Gonadotropin (hCG) and unconjugated Estriol (uE3). 9 When Inhibin A is added to these three biochemical markers, the detection rate of the test increases by 10% to about 75% and is called the Quadruple test. 10 Increased or decreased levels of the three serum markers can suggest the type of abnormality present. 11

A number of important factors can influence the results of the Triple test. These include: maternal age, race, weight, number of fetuses and gestational age. 3, 12 Women who have a positive screening test result for Down's syndrome are usually referred for genetic counseling and further testing.

In this article we describe the results of Triple tests carried out on Palestinian and non-Palestinian women who came to perform this test in different areas of the West Bank during the period 2004-2010.

Subjects and materials

Laboratory methods

All tests were performed in Zer laboratories in Jerusalem utilizing standardized techniques for analysis. Both AFP and hCG were performed using immunoradiometric assay (IRMA). AFP kit was produced by Byk-Santgtec Diagnostica-Germany, while the hCG kit was produced by ICN-USA. For uE3 the radioimmunoassay (RIA) kit used was a product of DSL-USA. ALPHA, which is special software for risk calculation was utilized in this study and produced by Logical Medical Systems, UK. The cut-off point utilized in this analysis was 1:380 at term risks.

Variables used in the study

The following variables were used: age at expected date of delivery, weight in kilograms, gestational age in weeks, *in vitro* fertilization (IVF) status, twins status, AFP levels in IU/mL and multiples of the normal gestation-specific median (MOM), hCG in IU/mL and MOM, uE3 in ng/mL and MOM. The variables were used to calculated risk for age alone and for the Triple test.

Statistical analysis

All data were entered into Statistical Package for Social Sciences (SPSS) version 17. Data cleaning was conducted and outliers were excluded, those included 29 twins pregnancies, 5 IVF, 1 unknown origin, and 52 Africans. A total 1267 cases were included in the final analysis. Basic descriptive statistics including means, medians, modes, standard deviation, and standard error were calculated. Frequencies were also calculated for relevant variables. Cross tabulations and Chi square test were used to explore the relation between different variables.

Results

Characteristics of the subjects

A total 1267 cases were investigated of which 88.4 % (1120) were Palestinian Arabs residing in the West Bank, while 11.6% (147) were non-Arabs (Filipinos). The mean expected age at delivery ± SE (standard error) of all subjects was 27.54±0.17 years while it was 27.02±0.17 years for Palestinian women and 31.47 ±0.45 years for Filipino women. 11.8% (150) of the participants were 35 years old or above. The mean weight for women at the time of testing was 65.79 ± 0.34 kilograms. The range of gestational age when the test was performed was 15 to 21 weeks, with a mean of 17.12 ±0.02.

Table 1: Mean serum concentrations of the three markers of the triple test. *Individual test results*

Characteristics	Concentration (Mean ± SE	
	Arabs (Palestinians) N=1120	Non Arabs (Filipinos) N=147
AFP	40.88±0.59	52.01±1.97
hCG	27.78±0.66	32.37±1.8
uE3	1.27±0.07	1.50±0.05

Table 2: Median serum concentration (MoM) and mean log_{10} for the 3 markers of the triple test *

Marker	Arabs (Palestinians) N=1120		Non Arabs (Filipinos) N=147	
	Median MoM (Interquartile Range)	Mean log_{10} MoM(SD)	Median MoM (Interquartile Range)	Mean log_{10} MoM(SD)
AFP	1.00 (0.76-1.29)	0.01 (0.22)	1.16 (0.91-1.48)	0.08 (0.20)
hCG	0.99 (0.65-1.46)	-0.01 (0.29)	1.04 (0.73-1.52)	0.02 (0.25)
uE3	1.06 (0.84-1.31)	0.02 (0.16)	1.28 (1.01-1.60)	0.09 (0.16)

* SD= standard deviation

Table 3: Triple test results for 1267 women and calculated risk by age group and origin

	Age (years)		Elevated AFP (%)	Elevated hCG (%)	Reduced hCG (%)	Reduced uE3 (%)	Calculated Risk (%)* (age+ triple test)	P-value (Risk)
Arabs	Age Group	15-24 n=448	2.5	3.6	0.9	0.2	2.2	0.000
		25-34 n=561	2.5	2.7	1.2	0.0	3.7	
		>35 n=111	4.5	2.7	0.0	0.0	22.5	
	Total(N=1120)		2.7	3.0	1.0	0.0	5.0	
Filipinos	Age Group	15-24 n=17	0.0	0.0	0.0	0.0	0.0	0.001
		25-34 n=91	3.3	3.3	1.1	0.0	2.2	
		>35 n=39	2.6	5.1	0.0	0.0	17.9	
	Total (N=147)		2.7	3.4	0.7	0.0	6.1	

Discussion

Palestinian pregnant women started showing interest in screening for Down's syndrome in the late 1990s. This is the second study performed in the Palestinian community in the last decade. In the period between 2004-2010, a group of Palestinian pregnant women were screened for Down's syndrome using the Triple test.

Neural tube defects (NTDs) are birth defects of the brain or spinal cord. In Jordan where a large number of Palestinians present for medical care - the NTD incidence was estimated to be 1.1 per 1000 births. 13 Screening for NTDs using maternal serum alpha-fetoprotein is used to identify women at increase risk of carrying of fetus with an NTD.14, 15 The most commonly used AFP MoM cutoff in the United States is 2.5 MoM, yielding initial screen-positive rate of 1% to 3%. 3 In this study, the AFP results of the Palestinian women tested using AFP MoM cutoff of 2.5 showed that 2.7% had high concentrations.

Filipino women showed the same result for AFP. These two results were in agreement with the initial screen-positive rate given for pregnant women in the United States.

The AFP results of this study were higher than those shown for Palestinian women in our first study published in 2005. 5 in which the proportion with high levels was 1.3% among a population of 943.

The Triple test was projected to detect about 60% of the Down's syndrome pregnancies by identifying 5% of all pregnant women as having a screen-positive test result, performance based on pregnancies being dated via LMP. 3 Our study showed that the total with high risk of Down's syndrome was 5%.

Comparing this result with that published in 2005, 5 where the proportion with high risk was 2.8%, there was a noticeable increase in this percentage. This may be due at least in part to difference in the mean expected age at delivery ± SE (standard error) which was 27.02±0.17 years compared with 25.5 ±0.2 years in the first study. This study showed also that for Filipino women the proportion with high risk of Down's syndrome was 6.1%. This higher value could also be attributed to age factor where the mean expected age at delivery of the Filipinos women sample was 31.47±0.45 years.

When comparing age groups (< 35 and ≥35) with risk, it was found that there was almost 7 folds increase in risk and it was statistically significant (*P*<0.00). This association stayed strong after controlling for ethnic origin (7 folds for Palestinian women and 9 folds for Filipinos).

When comparing the risk percentages for Down's syndrome of the total sample tested of both the Palestinian and Filipinos, there was no statistically significant difference in risk between them**.**

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Crown-Rump Length and Gestational Age

"The optimal gestational age for measurement of fetal NT is 11 weeks to 13 weeks 6 days. The minimum fetal crown-rump length should be 45mm and the maximum 84mm." (Nicolaides KH, www.fetalmedicine.com/fmf//FMF-English.pdf)

Although not explicitly stated, this equivalency of crown rump length (CRL) and gestational age (GA) appears to be based on the formula of Robinson and Fleming (1975) because this appears to give the closest match among the most commonly used conversion formulae available (see Table). But many MFM centers often do use the alternative conversions - including the newly recommended equation of Loughna *et al* (2009). The Table illustrates that there are differences for the various available formulae and these differences are most apparent for higher CRL pregnancies. The curve of Daya (1993) appears to be an outlier at higher CRL values but the other curves also vary by up to 4 days.

	≥ 45mm ≥ weeks + days	≤ 84mm ≤ weeks + days
Loughna *et al,* 2009	11 + 2	14 + 1
Kuhn *et al,* 1995	11 +2	14 + 0
Daya 1993	11 + 3	13 + 3
Hadlock et al 1992	11 + 3	14 + 2
Nelson 1981	11 + 1	14 + 3
Drumm 1977	11 + 2	14 + 2
Robinson and Fleming, 1975 (a)	11 + 1	13 + 6
Robinson and Fleming, 1975 (b)	11 + 0	14 + 0

(a) Based on the "point estimate" formula
(b) Based on a modified formula as described by Pedersen (1982)

The use of alternative conversions from CRL to GA poses several problems. First, it creates an ambiguity as to which patients are within an acceptable range for NT or serum test measurement. Should we use 45-84 mm or 11-13 weeks 6 days? If the latter, which curve should we use? Second, imprecise risk estimates can arise because the serum test normal median values (and sometimes NT medians) are based on GA rather than CRL. A laboratory may construct its medians based on data from heterogeneous conversions of CRL to GA derived from multiple MFM practices. It will then convert patients' results into MoMs on the basis of that heterogeneous data. But an individual woman's GA was based on a single method for dating that may depart from the consensus. Therefore, the MoMs can be inaccurate. Third, the statistical parameters in the risk calculation algorithm are also GA dependent reflecting the differences in efficacy of the screening at different times. An individual risk calculation could therefore also be based on statistical parameters that are not optimal for that particular patient. These difficulties will mostly affect cases that are screened close to the upper CRL/GA limit.

The problems could be minimized if normal median values and statistical parameters were routinely developed from a regression of the measurements against CRL rather than GA. It would also be very helpful if the Fetal Medicine Foundation FMF) and the Nuchal Translucency Quality Review (NTQR) program would provide a single recommendation for CRL/GA conversion and redefine (or reiterate) the recommended range for NT measurement.

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